



PCT/GB2003/005407



INVESTOR IN PEOPLE

The Patent Office  
Concept House  
Cardiff Road  
Newport  
South Wales  
NP10 8QQ

REC'D 03 FEB 2004

WIPO PCT

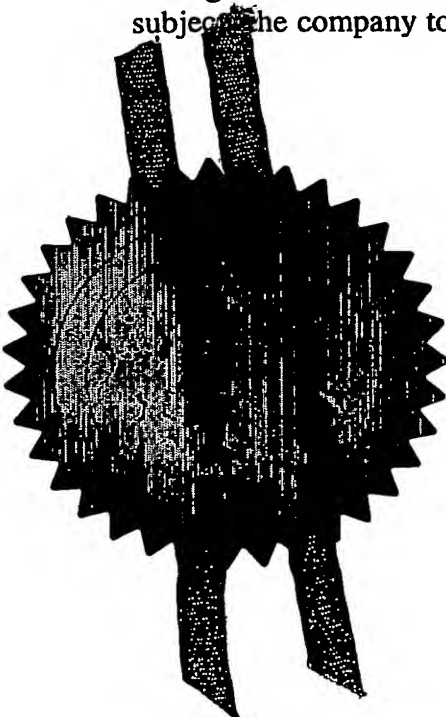
I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the application is now proceeding in the name as identified herein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed *AmBrewster*

Dated 22 January 2004

**PRIORITY  
DOCUMENT**

SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH RULE 17.1(a) OR (b)



INVESTOR IN PEOPLE

GB 0229673.9

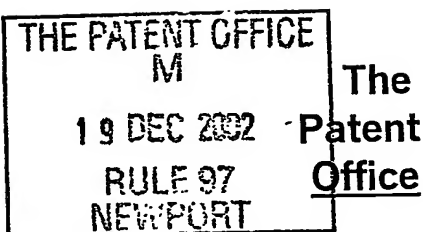
By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of:

VERNALIS (OXFORD) LIMITED,  
Watlington Road,  
OXFORD,  
OX4 5LY,  
United Kingdom

Incorporated in the United Kingdom,

[ADP No. 08740102001]

Patents Form 1/77  
Patents Act 1977  
Rules 16



1/77

The Patent Office

Cardiff Road  
Newport  
South Wales  
NP10 8QQ

# Request for grant of a patent

1. Your reference	242/AJW		
2. Patent application number	0229673.9		
3. Full name, address and postcode of the or of each applicant	British Biotech Pharmaceuticals Ltd Watlington Road Oxford OX4 6LY		
Patents ADP number	1742001		
If the applicant is a corporate body give the country/state of its corporation	GB		
4. Title of invention	Antibacterial Agents		
5. Name of your agent	Alan J. Walls		
Address for service in the United Kingdom to which all correspondence should be sent	British Biotech Pharmaceuticals Ltd Watlington Road Oxford OX4 6LY		
Patents ADP number	17442004		
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application no.	Date of filing (day/month/year)
	n/a	n/a	n/a
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier applications	Date of filing (day/month/year)	
	n/a	n/a	
8. Is a statement of inventorship and of right to grant of a patent required in support of this request?	Yes		

**Patents Form 1/77**

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form 0

Description 24

Claims(s) 8

Abstract 0

Drawing(s) 0

10. If you are also filing any of the following, state how many against each item.

Priority documents 0

Translations of priority documents 0

Statement of inventorship and right to grant a patent 0

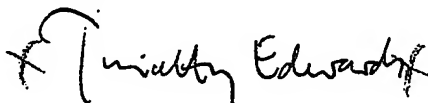
Request for preliminary examination 0

Request for substantive examination 0

Any other documents 0

11. I/We request the grant of a patent on the basis of this application.

Signature



Date

18/12/02

Timothy Edwards

Acting Chief Executive Officer

For and on behalf of British Biotech Pharmaceuticals Ltd

12. Name and daytime telephone number of person to contact in the United Kingdom

Alan J. Walls  
01865 748747

## Antibacterial Agents

This invention relates to novel hydroxamic acid and N-formyl hydroxylamine derivatives having antibacterial activity, to methods of treatment using such compounds, and to pharmaceutical and veterinary compositions comprising such compounds.

### Background to the Invention

Many classes of antibacterial agents are known, including the penicillins and cephalosporins, tetracyclines, sulfonamides, monobactams, fluoroquinolones and quinolones, aminoglycosides, glycopeptides, macrolides, polymyxins, lincosamides, trimethoprim and chloramphenicol. The fundamental mechanisms of action of these antibacterial classes vary.

Bacterial resistance to many known antibacterials is a growing problem. Accordingly there is a continuing need in the art for alternative antibacterial agents, especially those which have mechanisms of action fundamentally different from the known classes, and/or which are effective against the causative organisms of community acquired respiratory infections, and/or which are selective in their pharmacological activity, thus reducing risk of unwanted side effects.

Amongst the Gram-positive pathogens, such as staphylococci, streptococci, mycobacteria and enterococci, resistant strains have evolved/arisen which makes them particularly difficult to eradicate. Examples of such strains are methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase negative Staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiply resistant *Enterococcus faecium*.

### Brief Description of the Invention

This invention makes available a new class of hydroxamic acid and N-formyl hydroxylamine derivatives having antibacterial activity. The compounds are characterised inter alia by the presence of a hydrazide feature in their structural

backbone.

Although it may be of interest to establish the mechanism of action of the compounds with which the invention is concerned, it is their ability to inhibit bacterial growth that makes them useful. However, it is presently believed that their antibacterial activity is due, at least in part, to intracellular inhibition of bacterial polypeptide deformylase (PDF; EC 3.5.1.31).

#### Related Prior Art

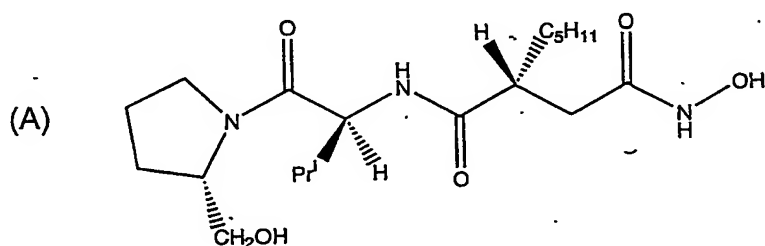
Although there are many publications disclosing both hydroxamic acid and N-formyl hydroxylamine derivatives as inhibitors of various metalloenzymes such as angiotensin converting enzyme, enkephalinase and the matrix metalloproteinases, there are relatively few relating to such compounds as antibacterial agents. The following patent publications are relevant in that connection:

WO 99/39704	(British Biotech)
WO 99/57097	(Versicor)
WO 99/59568	(British Biotech)
WO 00/35440	(British Biotech)
WO 00/44373	(British Biotech)
WO 00/58294	(British Biotech)
WO 00/61134	(British Biotech)
WO 01/10835	(British Biotech)
WO 01/38561	(Questcor)
WO 01/40198	(Aventis)
WO 01/42431	(Bayer)
WO 01/44178	(Versicor)
WO 01/44179	(Versicor)
WO 01/85160	(SmithKline Beecham)
WO 01/85170	(SmithKline Beecham)
WO 02/28829	(Questcor)
WO 02/41886	(British Biotech)

WO 02/50081 (British Biotech)

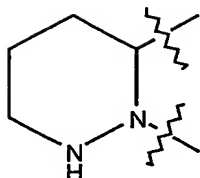
WO 02/070541 (SmithKline Beecham) relates to PDF inhibitor compounds which have a hydrazide feature in the backbone and an N-formylhydroxylamino metal binding group.

In addition the natural antibiotic actinonin (see for example J.C.S Perkin I, 1975, 819) is a hydroxamic acid derivative of Structure (A):



which is now known to act by inhibition of PDF. In addition to actinonin, various structural analogues of actinonin have also been shown to have antibacterial activity (see for example Devlin et al. *Journal of the Chemical Society. Perkin Transactions 1* (9):830-841, 1975; Broughton et al. *Journal of the Chemical Society. Perkin Transactions 1* (9):857-860, 1975).

The matlystatin group of compounds share a number of structural similarities with actinonin. Both are peptidic molecules with functional hydroxamic acid metal binding groups (Ogita et al., *J. Antibiotics*. 45(11):1723-1732; Tanzawa et al., *J. Antibiotics*. 45(11):1733-1737; Haruyama et al., *J. Antibiotics*. 47(12):1473-1480; Tamaki et al., *J. Antibiotics*. 47(12):1481-1492). The matlystatins and their close structural analogues are characterised by the presence in the molecule of a divalent piperazin-1, 6-diyl group, i.e.



In view of their close structural similarity to actinonin, the observation that actinonin inhibits PDF implies that matlystatin compounds may also inhibit PDF.

For a recent review of peptide deformylase inhibitors, see Clements et. al., Curr. Med. Chem. - Anti-Infective Agents, 2002, 1, 239-249.

The following patent publications disclose N-formyl hydroxylamine structures:

EP-B-0236872	(Roche)
WO 92/09563	(Glycomed)
WO 92/04735	(Syntex)
WO 95/19965	(Glycomed)
WO 95/22966	(Sanofi Winthrop)
WO 95/33709	(Roche)
WO 96/23791	(Syntex)
WO 96/16027	(Syntex/Agouron)
WO 97/03783	(British Biotech)
WO 97/18207	(DuPont Merck)
WO 98/38179	(GlaxoWellcome)
WO 98/47863	(Labs Jaques Logeais)

The pharmaceutical utility ascribed to the N-formyl hydroxylamine derivatives in those publications is the ability to inhibit matrix metalloproteinases (MMPs) and in some cases release of tumour necrosis factor (TNF), and hence the treatment of diseases or conditions mediated by those enzymes, such as cancer and rheumatoid arthritis.

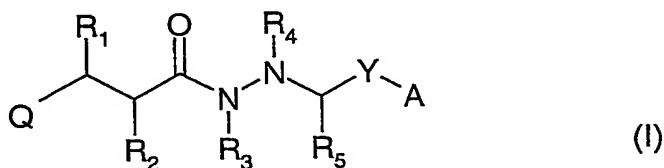


In addition to these, US-A-4,738,803 (Roques et al.) also discloses N-formyl hydroxylamine derivatives. However, these compounds are disclosed as enkephalinase inhibitors and are proposed for use as antidepressants and hypotensive agents. Also, WO 97/38705 (Bristol-Myers Squibb) discloses certain N-formyl hydroxylamine derivatives as enkephalinase and angiotensin converting enzyme inhibitors.

There are too many publications relating to metalloenzyme inhibiting hydroxylamic acid derivatives to summarise effectively. However a recent review, Whittaker et. al. Chem. Rev. 1999, 99, 2735, provides an overview of that art.

#### Description of the invention

The present invention provides a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof



wherein

Q represents a radical of formula  $-\text{N}(\text{OH})\text{CH}(\text{=O})$  or formula  $-\text{C}(\text{=O})\text{NH}(\text{OH})$ ;

Y represents  $-\text{C}(\text{=O})-$ ,  $-\text{C}(\text{=S})-$ ,  $-\text{S}(\text{=O})-$ , or  $-\text{SO}_2-$ ;

$\text{R}_1$  represents hydrogen,  $\text{C}_1$ - $\text{C}_6$  alkyl or  $\text{C}_1$ - $\text{C}_6$  alkyl substituted by one or more halogen atoms, or, except when Q is a radical of formula  $-\text{N}(\text{OH})\text{CH}(\text{=O})$ , a hydroxy,  $\text{C}_1$ - $\text{C}_6$  alkoxy,  $\text{C}_1$ - $\text{C}_6$  alkenyloxy, halogen, amino,  $\text{C}_1$ - $\text{C}_6$  alkylamino, or di-( $\text{C}_1$ - $\text{C}_6$  alkyl)amino group

$R_2$  represents a substituted or unsubstituted  $C_1-C_6$  alkyl,  $C_1-C_3$  alkyl- $O-C_1-C_3$  alkyl,  $C_1-C_3$  alkyl- $S-C_1-C_3$  alkyl, cycloalkyl( $C_1-C_3$  alkyl)-, aryl( $C_1-C_3$  alkyl)-, heterocyclyl( $C_1-C_3$  alkyl)-, or  $R^1R^2N-C_1-C_3$  alkyl group wherein  $R^1$  represents hydrogen or  $C_1-C_3$  alkyl and  $R^2$  represents  $C_1-C_3$  alkyl, or  $R^1R^2N-$  represents a cyclic amino group;

$R_3$  and  $R_5$  independently represent hydrogen or a substituted or unsubstituted  $C_1-C_6$  alkyl group or  $R_3$  and  $R_5$  taken together with the carbon and nitrogen atoms to which they are respectively attached form a saturated heterocyclic ring of from 5 to 7 ring atoms, which may be fused to a second carbocyclic or heterocyclic ring, either of which rings may optionally be substituted;

$R_4$  represents hydrogen or a substituted or unsubstituted  $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl, cycloalkyl, aryl, heterocyclyl,  $C_1-C_3$  alkyl- $O-C_1-C_3$  alkyl,  $C_1-C_3$  alkyl- $S-(C_1-C_3$  alkyl)-,  $C_1-C_3$  alkyl- $NH-(C_1-C_3$  alkyl)-, cycloalkyl( $C_1-C_3$  alkyl)-, heterocyclic( $C_1-C_3$  alkyl)- or aryl( $C_1-C_3$  alkyl)- group; and

$A$  represents a primary, secondary or tertiary amino group or a group  $-R_6$ ,  $-OR_6$ , wherein  $R_6$  is a substituted or unsubstituted  $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl, cycloalkyl, aryl, heterocyclyl,  $C_1-C_3$  alkyl- $O-(C_1-C_3$  alkyl)-,  $C_1-C_3$  alkyl- $S-(C_1-C_3$  alkyl)-,  $C_1-C_3$  alkyl- $NH-(C_1-C_3$  alkyl)-, cycloalkyl( $C_1-C_3$  alkyl)-, heterocyclic( $C_1-C_3$  alkyl)- or aryl( $C_1-C_3$  alkyl)- group.

In another aspect, the invention provides a method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound of formula (I) as defined above. Also included in the invention is the use of a compound of formula (I) as defined above for inhibiting bacterial growth in vitro and in vivo in mammals, and the use of such a compound for the manufacture of a composition for treating bacterial infection by inhibiting bacterial growth.

In a further aspect of the invention there is provided a method for the treatment of bacterial contamination by applying an antibacterially effective amount of a

compound of formula (I) as defined above to the site of contamination.

The compounds of formula (I) as defined above may be used as component(s) of antibacterial cleaning or disinfecting materials.

As used herein terms of the form " $(C_a-C_b)$ alkyl" where a and b are integers refer to a straight or branched chain alkyl moiety having from a to b carbon atoms. Thus, for example, the term " $(C_1-C_6)$ alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein terms of the form "divalent  $(C_a-C_b)$ alkylene radical" where a and b are integers refer to a saturated hydrocarbon chain having from a to b carbon atoms and two unsatisfied valencies.

As used herein terms of the form " $(C_a-C_b)$ alkenyl" where a and b are integers refer to straight or branched chain alkenyl moiety having from a to b carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. Thus, for example, the term " $(C_1-C_6)$ alkenyl" means a straight or chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond, and includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term " $C_a-C_b$  alkynyl" where a and b are integers refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. Thus, for example, the term " $(C_1-C_6)$ alkynyl" would include for example, ethynyl, 1-propynyl, 1- and 2-butyne, 2-methyl-2-propynyl, 2-pentyne, 3-pentyne, 4-pentyne, 2-hexyne, 3-hexyne, 4-hexyne and 5-hexyne.

As used herein the term "cycloalkyl" means a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic group, and to groups consisting of two covalently linked monocyclic carbocyclic aromatic groups. Illustrative of such groups are phenyl, biphenyl and naphthyl.

As used herein the term "heteroaryl" refers to a 5- or 6- membered aromatic ring containing one or more heteroatoms. Illustrative of such groups are thienyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular means a 5-7 membered aromatic or non-aromatic heterocyclic ring containing one or more heteroatoms selected from S, N and O, including for example, pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzofuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy, mercapto, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, nitro, -COOH, -CONH<sub>2</sub>, -COR<sup>A</sup>, -COOR<sup>A</sup>, -NHCOR<sup>A</sup>, -CONHR<sup>A</sup>, -NHR<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, or -CONR<sup>A</sup>R<sup>B</sup> wherein R<sup>A</sup> and R<sup>B</sup> are independently a (C<sub>1</sub>-C<sub>6</sub>)alkyl group.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

There are several actual or potential chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof. Currently, the preferred stereoconfiguration of the carbon atom carrying the  $R_2$  group is R.

In the compounds of the invention, in relation to the groups Q,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ , Y and A, separately and in combination:

#### The group Q

It is currently preferred that Q is an N-formyl hydroxylamine group  $-N(OH)CH(=O)$ .

#### The radical -Y-

It is currently preferred that -Y- is  $-C(=O)-$  or  $-SO_2-$ .

#### The group $R_1$

$R_1$  may be, for example, hydrogen, methyl, trifluoromethyl or, in the case where Q is a hydroxamic acid group  $HONHCO-$ , fluorine. Hydrogen is currently preferred.

#### The group $R_2$

$R_2$  may be, for example:

optionally substituted  $C_1-C_6$  alkyl,  $C_3-C_6$  alkenyl,  $C_3-C_6$  alkynyl or cycloalkyl;

phenyl( $C_1-C_6$  alkyl)-, phenyl( $C_3-C_6$  alkenyl)- or phenyl( $C_3-C_6$  alkynyl)-

optionally substituted in the phenyl ring;

cycloalkyl( $C_1-C_6$  alkyl)-, cycloalkyl( $C_3-C_6$  alkenyl)- or cycloalkyl( $C_3-C_6$  alkynyl)-

optionally substituted in the cycloalkyl ring; or

$CH_3(CH_2)_pO(CH_2)_q-$  or  $CH_3(CH_2)_pS(CH_2)_q-$ , wherein p is 0, 1, 2 or 3 and q is 1,

2 or 3.

Specific examples of  $R_2$  groups include

methyl, ethyl, n- and iso-propyl, n- and iso-butyl, n-pentyl, iso-pentyl, 3-methyl-but-1-yl, n-hexyl, n-heptyl, n-octyl, methylsulfanylethyl, ethylsulfanylmethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-ethoxymethyl, 3-hydroxypropyl, allyl, 3-phenylprop-3-en-1-yl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, but-2-yn-1-yl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, furan-2-ylmethyl, furan-3-methyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-2-ylmethyl, piperidinylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, and 4-methoxybenzyl.

Presently preferred groups at  $R_2$  are  $(C_1-C_6)$ alkyl-, cycloalkylmethyl-,  $(C_1-C_3)$ alkyl-S- $(C_1-C_3)$ alkyl-, or  $(C_1-C_3)$ alkyl-O- $(C_1-C_3)$ alkyl-, especially n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

#### The group $R_4$

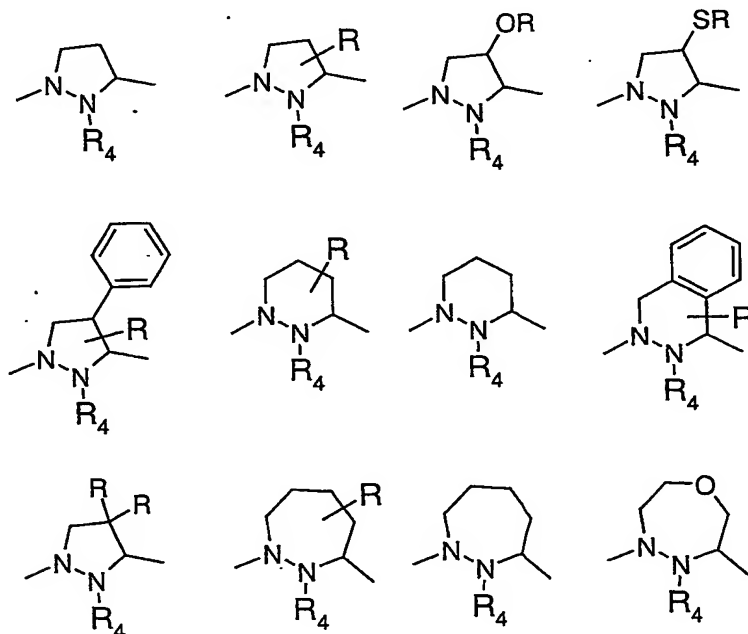
Examples of the group  $R_4$  include hydrogen,  $(C_1-C_6)$ alkyl-, cycloalkylmethyl-,  $(C_1-C_3)$ alkyl-S- $(C_1-C_3)$ alkyl-, or  $(C_1-C_3)$ alkyl-O- $(C_1-C_3)$ alkyl-, especially methyl, ethyl, n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

#### $R_3$ and $R_5$ when not part of a ring

When not part of a ring,  $R_3$  and  $R_5$  may independently be, for example, hydrogen,  $(C_1-C_6)$ alkyl-, cycloalkylmethyl-,  $(C_1-C_3)$ alkyl-S- $(C_1-C_3)$ alkyl-, or  $(C_1-C_3)$ alkyl-O- $(C_1-C_3)$ alkyl-, especially methyl, ethyl, n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

The ring formed by  $R_3$  and  $R_5$  and the nitrogens to which they are attached

Examples of rings which may be formed by  $R_3$  and  $R_5$  taken together with the carbon and nitrogen atoms to which they are respectively attached are the following, wherein  $R_4$  is as defined in relation to formula (I) and R represents hydrogen or  $C_1$ - $C_4$  alkyl:



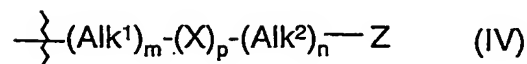
In the above rings, where a sulfur atom is present as a ring member, the equivalent structures wherein that sulfur is oxidised to  $-SO-$  or  $-SO_2-$  are also examples of ring structures which may be formed by  $R_3$  and  $R_5$ .

#### The group A

The group A is a primary, secondary or tertiary amino group or a group  $-R_6$ , or  $-OR_6$ . When A is  $-R_6$ , or  $-OR_6$ , the  $R_6$  group may be, for example, any of those given as  $R_2$  examples above, or a group of formula (II) as defined below, including such specific examples of groups (II) as morpholinyl, furanyl, thienyl, phenyl, and benzyl..

Presently it is preferred that A is a secondary or tertiary amino group, and in the latter case it may be a non-cyclic or a cyclic amino group. For example, A may be an

amino group of formula - NR<sub>6</sub>R<sub>7</sub> wherein R<sub>6</sub> and R<sub>7</sub> independently represent a radical of formula (IV)



wherein

m, p and n are independently 0 or 1;

Z represents hydrogen or a carbocyclic or heterocyclic ring of 5 to 7 ring atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 ring atoms;

Alk<sup>1</sup> and Alk<sup>2</sup> independently represent divalent C<sub>1</sub>-C<sub>3</sub> alkylene radicals;

X represents -O-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -C(=O)-, -NH-, -NR<sub>7</sub>- where R<sub>7</sub> is C<sub>1</sub>-C<sub>3</sub> alkyl;

and wherein

Alk<sup>1</sup>, Alk<sup>2</sup> and Z when other than hydrogen, independently are optionally substituted by

(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>2</sub>-C<sub>3</sub>)alkenyl, or (C<sub>2</sub>-C<sub>3</sub>)alkynyl,  
phenyl, optionally substituted by (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, halo, nitro,  
amino, mono- or di-(C<sub>1</sub>-C<sub>3</sub>)alkylamino, cyano or trifluoromethyl;

monocyclic 5 or 6-membered heterocyclic, optionally substituted by (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, halo, nitro, amino, mono- or di-(C<sub>1</sub>-C<sub>3</sub>)alkylamino, cyano or trifluoromethyl

benzyl, optionally substituted in the phenyl ring by (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, halo, nitro, amino, mono- or di-(C<sub>1</sub>-C<sub>3</sub>)alkylamino, cyano or trifluoromethyl,

hydroxy, phenoxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, or hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
mercapto, (C<sub>1</sub>-C<sub>6</sub>)alkylthio or mercapto(C<sub>1</sub>-C<sub>6</sub>)alkyl,



oxo,

nitro,

cyano

halo

-COOH, or -COOR<sup>A</sup>,

-CONH<sub>2</sub>, -CONHR<sup>A</sup>, or -CONR<sup>A</sup>R<sup>B</sup>

-COR<sup>A</sup>, -SO<sub>2</sub>R<sup>A</sup>,

-NHCOR<sup>A</sup>,

-NH<sub>2</sub>, -NHR<sup>A</sup>, or -NR<sup>A</sup>R<sup>B</sup>,

wherein R<sup>A</sup> and R<sup>B</sup> are independently a (C<sub>1</sub>-C<sub>6</sub>) alkyl group, R<sup>A</sup> and R<sup>B</sup> taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring which may be substituted by (C<sub>1</sub>-C<sub>3</sub>)alkyl, hydroxy, or hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl.

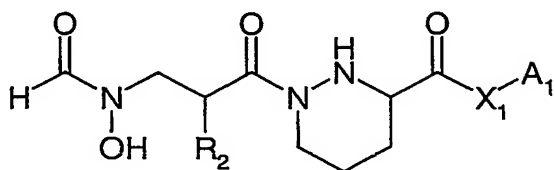
The amino group A may also be one of formula -NR<sub>8</sub>R<sub>9</sub> wherein R<sub>8</sub> and R<sub>9</sub> when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring of 5 to 8 atoms optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 ring atoms, any of which rings being optionally substituted by a radical of formula (IV) as defined above. Examples of cyclic amino groups are 1-pyrrolidinyl, piperidin-1-yl, 1-piperazinyl, hexahydro-1-pyridazinyl, morpholin-4-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl 1-oxide, tetrahydro-1,4-thiazin-4-yl 1,1-dioxide, hexahydroazipino, thiomorpholino, diazepino, and thiazolidinyl. Presently preferred are piperidin-1-yl and 1-piperazinyl.

#### The group of formula (IV)

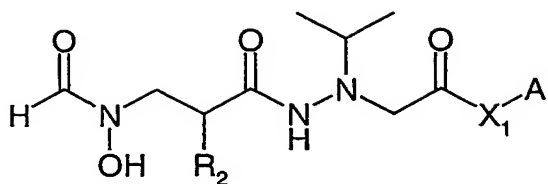
In the substituent (IV) Alk<sup>1</sup> and Alk<sup>2</sup> may independently represent, for example -(CH<sub>2</sub>)- or -(CH<sub>2</sub>CH<sub>2</sub>)-. In the case where m is 0 and p is 1, X may be, for example -S-, -S(=O)-, or preferably -C(=O)- or -S(O<sub>2</sub>)-. In such cases n may be 0 or 1

Compounds of the invention include those selected from the group consisting of

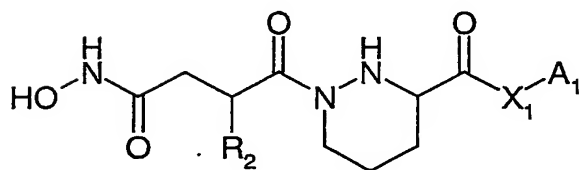
compounds of formulae (IIA) - (IID).



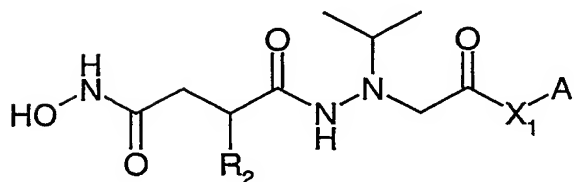
(IIA)



(IIB)



(IIC)



(IID)

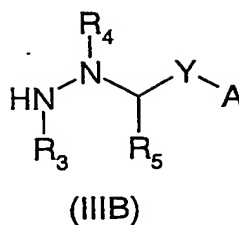
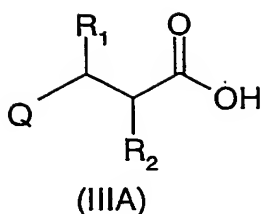
wherein  $R_2$  is as defined in relation to formula (IV), especially n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl;

$X_1$  is a bond,  $C_1$ - $C_3$  alkylene, -NH- or -O-; and

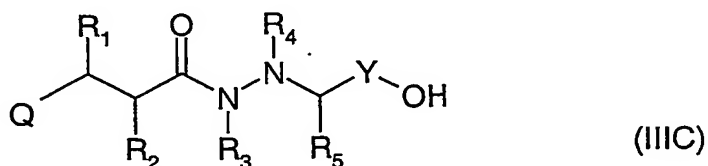
$A_1$  is optionally substituted  $C_1$ - $C_6$  alkyl, cycloalkyl, aryl, or heterocyclic, for example methyl, ethyl phenyl, cyclopentyl, cyclohexyl, 2- or 3-furanyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-oxazolyl, or 3-, 4- or 5-thiazolyl, methoxymethyl, 3,5-bis-(trifluoromethyl)phenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 3,4-methylenedioxyphenyl, 4-fluorophenyl benzyl, 3-pyridyl, 4-pyridyl, cyclohexyl, 1,3-dimethylpyrazol-5-yl, 1-methylimidazol-5-yl, and 2-[morpholin-1-yl]pyrid-5-yl.

Particular compounds of the invention include those of the Examples herein.

In general, compounds of the invention are accessible by conventional synthetic procedures. For example, they may be prepared by condensation of an acid of formula (IIIA) with a hydrazide of formula (IIIB):



In addition, compounds wherein A is a primary, secondary or tertiary amino group may be prepared by condensation of a compound of formula (III) or an activated derivative thereof with the appropriate amine:



As is conventional, any reactive constituents of the intermediates used in the above reactions may be protected during the condensation reaction and deprotected subsequently.

The Examples herein provide further details of routes and methods for the preparation of compounds of the invention.

Compositions with which the invention is concerned may be prepared for administration by any route consistent with the pharmacokinetic properties of the active ingredient(s).

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or

polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Safe and effective dosages for different classes of patient and for different disease states will be determined by clinical trial as is required in the art. It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following examples illustrate embodiments of the invention.

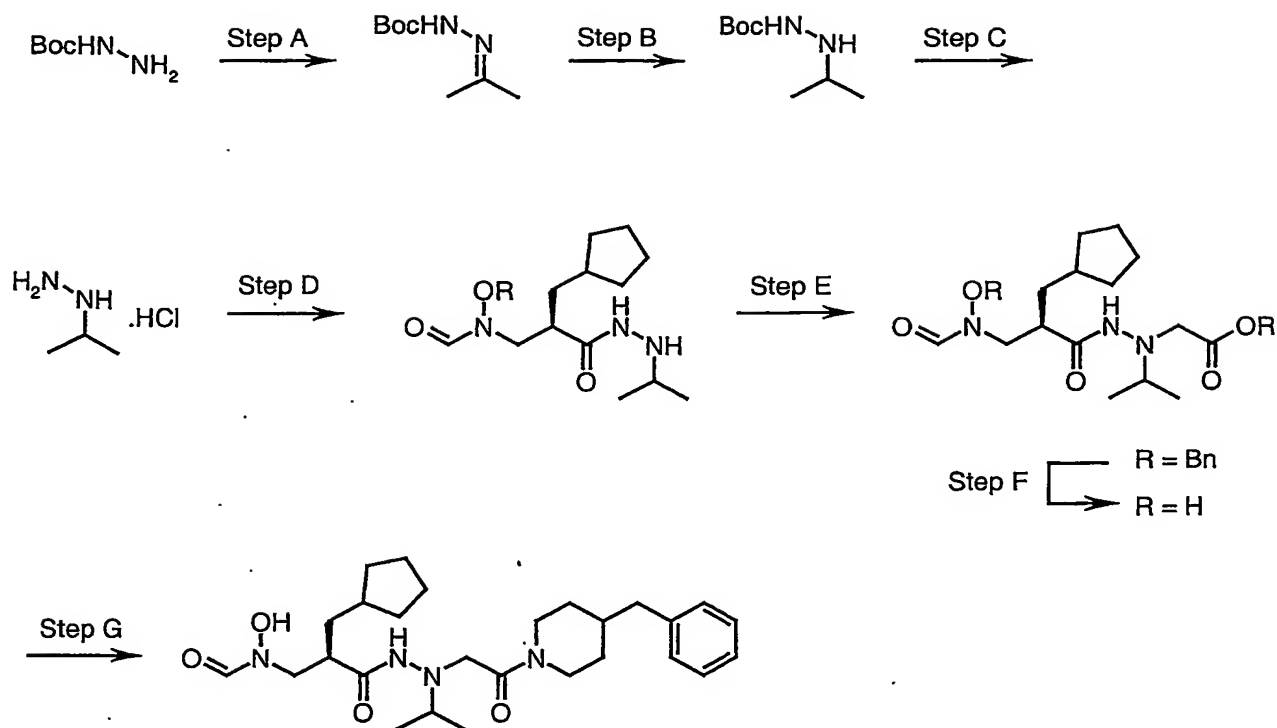
In the Examples, the following abbreviations have been used:

DMF	Dimethylformamide
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
LRMS	Low resolution mass spectrometry

NMR	Nuclear magnetic resonance
RT	Retention Time
TLC	Thin layer chromatography
DIEA	N,N-diisopropylethylamine
DCM	Dichloromethane
HATU	O-(7-Azabenzotriazo-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded using a Bruker DPX 250 spectrometer at 250.1 and 62.9MHz, respectively. Mass spectra were obtained using a Perkin Elmer Sciex API 165 spectrometer using both positive and negative ionisation modes. Infra-red spectra were recorded on a Perkin Elmer PE 1600 FTIR spectrometer. Analytical HPLC was performed on a Beckman System Gold, using Waters Nova Pak C18 column (150 mm, 3.9 mm) with 20 to 90 % solvent B gradient (1 ml/min) as the mobile phase. [Solvent A: 0.05% TFA in 10% water 90% methanol; Solvent B: 0.05% TFA in 10% methanol 90%], detection wavelength at 230 nm. Preparative HPLC was performed on a Gilson autoprep instrument using a C18 Waters delta prep-pak cartridge (15 $\mu\text{m}$ , 300 A, 25 mm, 10 mm) with 20 to 90 % solvent B gradient (6 ml/min) as the mobile phase. [Solvent A water; Solvent B: methanol], UV detection was at 230 nm.

## Example 1



Step A: acetone,  $\text{NaBH}(\text{OAc})_3$ , THF, rt, 16 h; Step B:  $\text{H}_2$ , 5% Pt/C, MeOH, 1.45 h; Step C: 4M HCl, 1,4-dioxane, rt, 2 h; Step D: 3-benzyloxyformylamino-(2*R*)-cyclopentylmethyl propionic acid, HATU, collidine, DCM, 0°C, 15 min, *then* hydrazine, 0°C, 1 h; Step E: benzyl 2-bromoacetate, DIEA,  $\text{CH}_2\text{Cl}_2$ , 45°C, 16 h; Step F:  $\text{H}_2$  (g), 10% Pd/C, MeOH, rt, 2 h; Step G: EDAC, HOAt, DCM, 0°C, 15 min, *then* 4-benzyl piperidine, 0°C to rt, 16 h.

## Step A:

## Isopropylidene hydrazine

To a solution of *tert*-butyl carbazate (2.64 g, 20 mmol) in THF (50 ml) at rt under argon was added acetone (1.61 ml, 22 mmol) and sodium triacetoxyborohydride (4.45 g, 22 mmol). The resulting suspension was stirred for 16 h. After this time the mixture was concentrated under reduced pressure and the crude product was partitioned between EtOAc and sat.  $\text{NaHCO}_3$ . The organic layer was separated, washed with sat. NaCl, dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced

pressure to give a pale yellow oil. This oil was purified by chromatography on silica eluting with 50% EtOAc/hexanes to give the title compound as a white solid (2.95 g, 85%).  $^1\text{H-NMR}$ ;  $\delta(\text{CDCl}_3)$ , 7.34 (1H, s, NH), 2.04 (3H, s,  $\text{CH}_3$ ), 1.81 (3H, s,  $\text{CH}_3$ ), 1.51 (9H, s,  $(\text{CH}_3)_3$ ). LRMS: +ve ion: 195  $[\text{M}+23]$ , 117.

#### Step B:

*N*-(Isopropyl)-hydrazine carboxylic acid *tert*-butyl ester

To a solution of isopropylidene hydrazine (2.94 g, 17.1 mmol) in MeOH at rt under argon was added 5% Pt/C (290 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 1.5 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure. The crude material that remained was then redissolved in EtOAc and washed with sat.  $\text{NaHCO}_3$ . The organic layer was separated, washed with sat. NaCl, dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. Purification by chromatography on silica eluting with 50% EtOAc/hexanes gave the title compound as colourless crystals (2.08 g, 70%).  $^1\text{H-NMR}$ ;  $\delta(\text{CDCl}_3)$ , 6.34 (1H, s,  $\text{NH-Boc}$ ), 3.50 (1H, br, NH) 3.13 (1H, sept,  $J=6.5\text{Hz}$ ;  $\text{CH}(\text{CH}_3)_2$ ), 1.46 (9H, s,  $(\text{CH}_3)_3$ ), 1.02 (6H, d,  $J=6.5\text{Hz}$ ,  $(\text{CH}_3)_2\text{CH}$ ). LRMS: +ve ion: 197  $[\text{M}+23]$ , 175  $[\text{M}+1]$ , 161.

#### Step C:

Isopropyl hydrazine hydrochloride

To *N*-(Isopropyl)-hydrazine carboxylic acid *tert*-butyl ester (1.26 g, 7.24 mmol) at rt in air was added 4M HCl in 1,4-dioxane (25 ml). The mixture was stirred for 2 h and then concentrated under reduced pressure to give a white solid which was used in the next step (assumed quantitative yield, 7.24 mmol).

#### Step D:

*N*-Benzyloxy-*N*-[3-cyclopentyl-(2*R*)-(N-isopropylhydrazinocarbonyl)-propyl]-formamide

To a solution of the 3-benzyloxyformylamino-(2*R*)-cyclopentylmethyl propionic acid

(190 mg, 0.62 mmol) in DCM (5 ml) at 0°C under argon was added HATU (237 mg, 0.62 mmol) followed by collidine (165 µl, 2.49 mmol). The resulting mixture was stirred for 5 min at rt before the amine hydrochloride (69 mg, 0.62 mmol) was added as a solution in DCM (1 ml) and collidine (165 µl, 2.49 mmol). The reaction was stirred at 0°C for 1 h and then the mixture was concentrated under reduced pressure. The crude material was partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organics were separated, washed with sat. NaCl, dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure to give an oil. This oil was purified by chromatography on silica eluting with 70-100% EtOAc/hexanes to give the title compound as a colourless oil (119 mg, 53%). <sup>1</sup>H-NMR; δ(CDCl<sub>3</sub>), 8.12 (0.67H, s, CHO), 7.86 (0.33H, br s, CHO), 7.5-7.3 (6H, br m, ArH and NH), 4.9-4.6 (2H, br m, OCH<sub>2</sub>Ph), 3.8-3.6 (2H, br m, CH<sub>2</sub>NO), 3.01 (1H, sept, J=6.5Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 2.5-2.4 (1H, m, CHCO), 1.8-1.3 (9H, m), 1.2-0.9 (2H, m), 0.98 (6H, d, J=6.5Hz, (CH<sub>3</sub>)<sub>2</sub>CH). LRMS: +ve ion: 362 [M+1].

#### Step E:

{*N*-[3-(Benzyloxy-formyl-amino)-(2*R*)-cyclopentylmethyl-propionyl]-*N*-isopropylhydrazino}acetic acid benzyl ester

To *N*-benzyloxy-*N*-[3-cyclopentyl-(2*R*)-(N-isopropylhydrazinocarbonyl)-propyl]-formamide (69 mg, 0.191 mmol) in DCM (2.5 ml) under argon was added benzyl 2-bromoacetate (30 µl, 0.19 mmol) followed by DIEA (33 µl, 0.19 mmol). The reaction was stirred at 45°C for 16 h. After this time, methylisocyanate polystyrene resin (198 mg, 0.09 mmol)(200-400 mesh, 1.45 mmol/g) was added and the mixture shaken for 12 h. The mixture was filtered and concentrated under reduced pressure to give a crude product which was purified by chromatography on silica eluting with EtOAc to give the title compound as a colourless oil (32 mg, 33%). <sup>1</sup>H-NMR; δ(CDCl<sub>3</sub>), 8.1-7.8 (1H, m, CHO), 7.6-7.2 (10H, m, 2 x Ph), 5.3-5.0 (2H, m, NOCH<sub>2</sub>), 5.0-4.6 (2H, m, NCH<sub>2</sub>CO), 3.8-3.5 (4H, m, CH<sub>2</sub>NO and CO<sub>2</sub>CH<sub>2</sub>), 3.3-3.1 (1H, m, CH(CH<sub>3</sub>)<sub>2</sub>), 3.1-2.4 (1H, br m, COCH<sub>2</sub>CH<sub>2</sub>), 1.9-0.8 (11H, m), 1.04 (6H, d, J=6.5Hz, CH(CH<sub>3</sub>)<sub>2</sub>); LRMS: +ve ion: 532 [M+23], 510 [M+1].

#### Step F:



{*N*-[(2*R*)-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-*N*-isopropyl-hydrazino}acetic acid

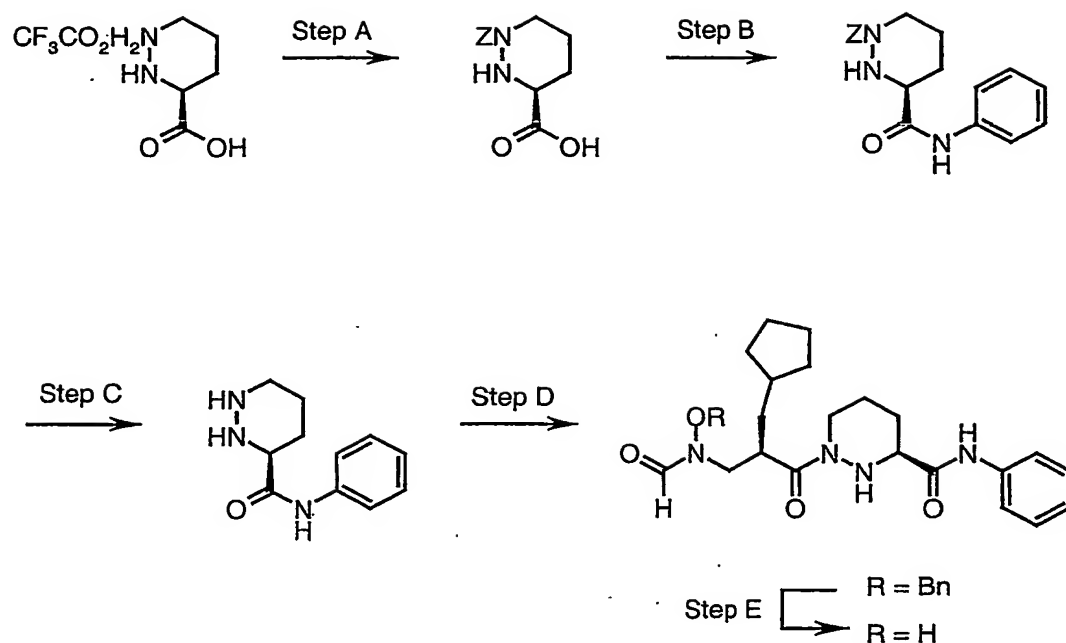
To a solution of the {*N*-[3-(benzyloxy-formyl-amino)-(2*R*)-cyclopentylmethyl-propionyl]-*N*-isopropyl-hydrazino}acetic acid benzyl ester (31 mg, 0.061 mmol) in EtOH at rt under argon was added 10% Pd/C (5 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 1 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give a colourless oil (18 mg, 92%). <sup>1</sup>H-NMR; δ (CD<sub>3</sub>OD), 8.23 (0.3H, s, CHO), 7.84 (0.7H, s, CHO), 3.9-2.6 (6H, m), 1.9-0.9 (17H, m). LRMS: +ve ion: 352 [M+23], 330 [M+1].

#### Step G:

*N*-(2-{*N*-[(2*R*)-(4-Benzyl-piperidin-1-yl)-2-oxo-ethyl]-*N'*-isopropyl-hydrazinocarbonyl]-3-cyclopentyl propyl)-*N*-hydroxy formamide

To a solution of {*N*-[(2*R*)-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-*N*-isopropyl-hydrazino}acetic acid (18 mg, 0.055 mmol) in DMF (2 ml) at 0°C under argon was added EDAC (13 mg, 0.066 mmol) and HOAt (11 mg, 0.083 mmol). The resulting mixture was stirred for 15 min before 4-benzylpiperidine (11 µl, 0.083 mmol) was added. The reaction was stirred for 15 min at 0°C and then warmed to rt where it was maintained for 16 h. The reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (x2) and the combined organics washed with sat. NaCl, dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure to give an oil. Purification by preparative HPLC gave the title compound as a colourless oil (6 mg, 22%). <sup>1</sup>H-NMR; δ(CD<sub>3</sub>OD), 8.23 (0.33H, s, CHO), 7.84 (0.67H, s, CHO), 7.3-7.0 (5H, m, Ph), 4.5-4.0 (2H, m, CH<sub>2</sub>CO), 3.8-2.6 (8H, m), 2.6-2.5 (2H, m, CH<sub>2</sub>Ph), 1.9-0.9 (22H, m). LRMS: +ve ion: 362 [M+1].

## Example 2



Step A:  $\text{PhCH}_2\text{OCOCl}$ , 1M NaOH (aq), PhMe, 0 °C; Step B: EDAC.HCl, HOAt, aniline, DMF 0 °C to rt; Step C:  $\text{H}_2$ , 10% Pd/C, EtOH; Step D: 3-benzyloxyformylamino-(2*R*)-cyclopentylmethyl propionic acid, EDAC.HCl, HOAt, 0 °C, 15 min, *then* piperazine acid amide, 0 °C to rt; Step E:  $\text{H}_2$  (g), 10% Pd/C, EtOH, rt, 2 h.

## Step A:

Tetrahydro-pyridazine-(1,3*S*)-dicarboxylic acid 1-benzyl ester

To a solution of (3*S*)-piperazine acid trifluoroacetic acid salt (129 mg, 0.53 mmol) in toluene/1M NaOH (1:1, 4 ml) at rt under argon was added benzyl chloroformate (114  $\mu\text{l}$ , 0.79 mmol). The resulting solution was stirred for 1 h. After this time the mixture was diluted with water, washed with  $\text{Et}_2\text{O}$  (x3) and acidified to pH 5 with 1M HCl. The aqueous fraction was then extracted with EtOAc (x3), dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure to give a crude product as a white solid (125 mg, 89%).  $^1\text{H-NMR}$ ;  $\delta(\text{CD}_3\text{OD})$ , 7.5-7.2 (5H, m, Ph), 5.12 (2H, s,  $\text{CH}_2\text{Ph}$ ), 4.0-3.8 (1H, m,  $\text{NCH}_\text{A}\text{H}_\text{B}$ ), 3.6-3.5 (1H, m,  $\text{NCHCO}_2$ ), 3.3-3.1 (1H, m,  $\text{NCH}_\text{A}\text{H}_\text{B}$ ), 2.1-2.0

(1H, m), 1.8-1.5 (3H, m). LRMS: +ve ion: 287 [M+23], 265 [M+1].

#### Step B:

(3*S*)-Phenylcarbamoyl-tetrahydro-pyridazine-1-carboxylic acid benzyl ester

To a solution of tetrahydro-pyridazine-(1,3*S*)-dicarboxylic acid 1-benzyl ester (85 mg, 0.32 mmol) in DMF (2 ml) at 0°C under argon was added EDAC (74 mg, 0.39 mmol) and HOAt (66 mg, 0.48 mmol). The resulting mixture was stirred for 15 min before aniline (32  $\mu$ L, 0.35 mmol) was added. The reaction was stirred for 15 min at 0°C and then warmed to rt where it was maintained for 16 h. The reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (x2) and the combined organics washed with sat. NaHCO<sub>3</sub>, sat. NaCl, dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure to give a crude product as an oil. Purification by chromatography on silica eluting with 30% EtOAc/hexane gave the title compound as a colourless oil (83 mg, 76%). <sup>1</sup>H-NMR;  $\delta$ (CD<sub>3</sub>OD), 7.7-7.4 (2H, br s, ArH), 7.4-7.2 (7H, m, ArH), 7.07 (1H, t, J=7.5Hz, ArH), 5.20 (1H, d, J=5Hz, OCH<sub>A</sub>H<sub>B</sub>Ph), 5.11 (1H, d, J=5Hz, OCH<sub>A</sub>H<sub>B</sub>Ph), 3.82 (1H, dt, J=13 and 5Hz, NCH<sub>A</sub>H<sub>B</sub>), 3.69 (1H, t, J=5Hz, NCHCO), 3.4-3.2 (1H, m, NCH<sub>A</sub>H<sub>B</sub>), 2.3-2.1 (1H, m), 1.9-1.4 (3H, m). LRMS: +ve ion: 362 [M+23].

#### Step C:

Hexahydro-pyridazine-(3*S*)-carboxylic acid phenylamide

To a solution of the (3*S*)-phenylcarbamoyl-tetrahydro-pyridazine-1-carboxylic acid benzyl ester (83 mg, 0.25 mmol) in EtOH at rt under argon was added 10% Pd/C (8 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 1 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give a colourless oil (49 mg, 98%) which was used immediately for the next step. LRMS: +ve ion: 228 [M+23], 206 [M+1].

#### Step D:

1-[(2*R*)-(Benzyloxy-formyl-amino)-methyl]-3-cyclopentyl-propionyl]-hexahydro-

pyridazine-(3*S*)-carboxylic acid phenylamide

To a solution of 3-benzyloxyformylamino-(2*R*)-cyclopentylmethyl propionic acid (44 mg, 0.15 mmol) in DMF (3 ml) at 0°C under argon was added EDAC (30 mg, 0.16 mmol) and HOAt (27 mg, 0.19 mmol). The resulting mixture was stirred for 15 min before a solution of hexahydro-pyridazine-(3*S*)-carboxylic acid phenylamide (27 mg, 0.13 mmol) in DMF (0.5 ml) was added. The reaction was stirred for 15 min at 0°C and then warmed to rt where it was maintained for 16 h. The reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (x2) and the combined organics washed with sat. NaCl, dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure to give an oil. This oil was purified by chromatography on silica eluting with EtOAc to give the title compound as a colourless oil (18 mg, 25%). <sup>1</sup>H-NMR; δ(CDCl<sub>3</sub>), 9.56 (1H, br s, NH), 8.4-7.9 (1H, m, CHO), 7.8-7.0 (10H, m, ArH), 5.1-4.5 (3H, m), 4.0-3.0 (5H, m), 2.5-0.9 (15H, m). LRMS: +ve ion: 515 [M+23].

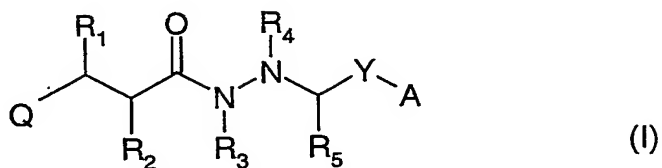
Step E:

1-[(2*R*)-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl]-hexahydro-pyridazine-(3*S*)-carboxylic acid phenylamide

To a solution of the 1-[(2*R*)-(benzyloxy-formyl-amino)-methyl]-3-cyclopentyl-propionyl]-hexahydro-pyridazine-(3*S*)-carboxylic acid phenylamide (18 mg, 0.037 mmol) in EtOH (2 ml) at rt under argon was added 10% Pd/C (4 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 1 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give a colourless oil. This oil was purified by preparative HPLC to give the title compound as a colourless oil (8 mg, 50%). <sup>1</sup>H-NMR; δ (CD<sub>3</sub>OD), 8.26 (0.4H, s, CHO), 7.85 (0.6H, s, CHO), 7.7-7.5 (2H, m, ArH), 7.29 (2H, t, J=7.5Hz, ArH), 7.11 (1H, t, J=7.5Hz, ArH), 4.5-4.4 (1H, m, NCHCON), 4.2-3.2 (4H, m), 2.9-2.7 (1H, m), 2.2-0.8 (15H, m). LRMS: +ve ion: 425 [M+23], 403 [M+1].

## Claims:

1. a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof



wherein

Q represents a radical of formula  $-N(OH)CH(=O)$  or formula  $-C(=O)NH(OH)$ ;

Y represents  $-C(=O)-$ ,  $-C(=S)-$ ,  $-S(=O)-$ , or  $-SO_2-$ ;

$R_1$  represents hydrogen,  $C_1-C_6$  alkyl or  $C_1-C_6$  alkyl substituted by one or more halogen atoms, or, except when Q is a radical of formula  $-N(OH)CH(=O)$ , a hydroxy,  $C_1-C_6$  alkoxy,  $C_1-C_6$  alkenyloxy, halogen, amino,  $C_1-C_6$  alkylamino, or di- ( $C_1-C_6$  alkyl)amino group

$R_2$  represents a substituted or unsubstituted  $C_1-C_6$  alkyl,  $C_1-C_3$  alkyl-O- $C_1-C_3$  alkyl,  $C_1-C_3$  alkyl-S- $C_1-C_3$  alkyl, cycloalkyl( $C_1-C_3$  alkyl)-, aryl( $C_1-C_3$  alkyl)-, heterocyclyl( $C_1-C_3$  alkyl)-, or  $R^1R^2N$ - $C_1-C_3$  alkyl group wherein  $R^1$  represents hydrogen or  $C_1-C_3$  alkyl and  $R^2$  represents  $C_1-C_3$  alkyl, or  $R^1R^2N$ - represents a cyclic amino group;

$R_3$  and  $R_5$  independently represent hydrogen or a substituted or unsubstituted  $C_1-C_6$  alkyl group or  $R_3$  and  $R_5$  taken together with the carbon and nitrogen atoms to which they are respectively attached form a saturated heterocyclic ring of from 5 to 7 ring atoms, which may be fused to a second carbocyclic or heterocyclic ring, either of which rings may optionally be substituted;

$R_4$  represents hydrogen or a substituted or unsubstituted  $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,

C<sub>2</sub>-C<sub>6</sub> alkynyl, cycloalkyl, aryl, heterocyclyl, C<sub>1</sub>-C<sub>3</sub> alkyl-O-C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkyl-S-(C<sub>1</sub>-C<sub>3</sub> alkyl)-, C<sub>1</sub>-C<sub>3</sub> alkyl-NH-(C<sub>1</sub>-C<sub>3</sub> alkyl)-, cycloalkyl(C<sub>1</sub>-C<sub>3</sub> alkyl)-, heterocyclic(C<sub>1</sub>-C<sub>3</sub> alkyl)- or aryl(C<sub>1</sub>-C<sub>3</sub> alkyl)- group; and

A represents a primary, secondary or tertiary amino group or a group -R<sub>6</sub>, -OR<sub>6</sub>, wherein R<sub>6</sub> is a substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, cycloalkyl, aryl, heterocyclyl, C<sub>1</sub>-C<sub>3</sub> alkyl-O-(C<sub>1</sub>-C<sub>3</sub> alkyl)-, C<sub>1</sub>-C<sub>3</sub> alkyl-S-(C<sub>1</sub>-C<sub>3</sub> alkyl)-, C<sub>1</sub>-C<sub>3</sub> alkyl-NH-(C<sub>1</sub>-C<sub>3</sub> alkyl)-, cycloalkyl(C<sub>1</sub>-C<sub>3</sub> alkyl)-, heterocyclic(C<sub>1</sub>-C<sub>3</sub> alkyl)- or aryl(C<sub>1</sub>-C<sub>3</sub> alkyl)- group.

2. A compound as claimed in claim 1 wherein Q is an N-formyl hydroxylamine group -N(OH)CH(=O).

3. A compound as claimed in claim 1 or claim 2 wherein -Y- is -C(=O)- or -SO<sub>2</sub>-.

4. A compound as claimed in any of the preceding claims wherein R<sub>1</sub> is hydrogen.

5. A compound as claimed in any of the preceding claims wherein R<sub>2</sub> is

optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> alkynyl or cycloalkyl;

phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, phenyl(C<sub>3</sub>-C<sub>6</sub> alkenyl)- or phenyl(C<sub>3</sub>-C<sub>6</sub> alkynyl)- optionally substituted in the phenyl ring;

cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, cycloalkyl(C<sub>3</sub>-C<sub>6</sub> alkenyl)- or cycloalkyl(C<sub>3</sub>-C<sub>6</sub> alkynyl)- optionally substituted in the cycloalkyl ring; or

CH<sub>3</sub>(CH<sub>2</sub>)<sub>p</sub>O(CH<sub>2</sub>)<sub>q</sub>- or CH<sub>3</sub>(CH<sub>2</sub>)<sub>p</sub>S(CH<sub>2</sub>)<sub>q</sub>-, wherein p is 0, 1, 2 or 3 and q is 1, 2 or 3.

6. A compound as claimed in any of claims 1 to 4 wherein R<sub>2</sub> is methyl, ethyl, n-

or iso-propyl, n- or iso-butyl, n-pentyl, iso-pentyl, 3-methyl-but-1-yl, n-hexyl, n-heptyl, n-octyl, methylsulfanylethyl, ethylsulfanylmethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-ethoxymethyl, 3-hydroxypropyl, allyl, 3-phenylprop-3-en-1-yl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, but-2-yn-1-yl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, furan-2-ylmethyl, furan-3-ylmethyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-2-ylmethyl, piperidinylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, or 4-methoxybenzyl.

7. A compound as claimed in any of claims 1 to 4 wherein  $R_2$  is  $(C_1-C_6)$ alkyl-, cycloalkylmethyl-,  $(C_1-C_3)$ alkyl-S- $(C_1-C_3)$ alkyl-, or  $(C_1-C_3)$ alkyl-O- $(C_1-C_3)$ alkyl-.

8. A compound as claimed in claim 7 wherein  $R_2$  is n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

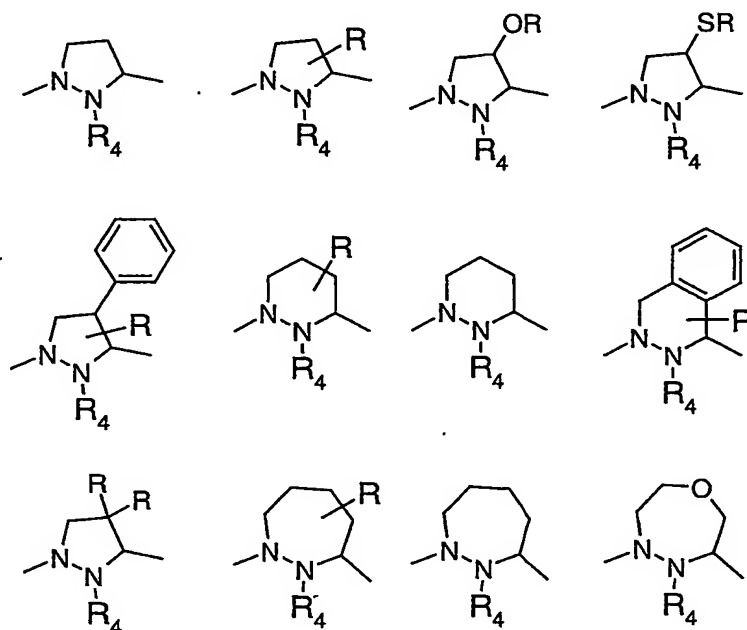
9. A compound as claimed in any of the preceding claims wherein  $R_4$  is hydrogen,  $(C_1-C_6)$ alkyl-, cycloalkylmethyl-,  $(C_1-C_3)$ alkyl-S- $(C_1-C_3)$ alkyl-, or  $(C_1-C_3)$ alkyl-O- $(C_1-C_3)$ alkyl-.

10. A compound as claimed in claim 9 wherein  $R_4$  is hydrogen, methyl, ethyl, n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

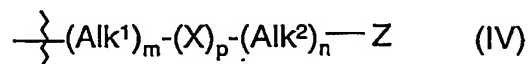
11. A compound as claimed in any of the preceding claims wherein  $R_3$  and  $R_5$ , when not part of a ring, are independently hydrogen,  $(C_1-C_6)$ alkyl-, cycloalkylmethyl-,  $(C_1-C_3)$ alkyl-S- $(C_1-C_3)$ alkyl-, or  $(C_1-C_3)$ alkyl-O- $(C_1-C_3)$ alkyl-.

12. A compound as claimed in claim 11 wherein  $R_3$  and  $R_5$  are independently hydrogen, methyl, ethyl, n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

13. A compound as claimed in any of claims 1 to 10 wherein  $R_3$  and  $R_5$  taken together with the carbon and nitrogen atoms to which they are respectively attached form the following rings, wherein any sulfur atom present as a ring member may be oxidised to  $-SO-$  or  $-SO_2-$ ,  $R_4$  is as defined in any preceding claim, and  $R$  represents hydrogen or  $C_1$ - $C_4$  alkyl:



14. A compound as claimed in any of the preceding claims wherein A a group  $-NR_6R_7$ ,  $-R_6$ , or  $-OR_6$  wherein  $R_6$  and  $R_7$  independently represent a radical of formula (IV)



wherein

$m$ ,  $p$  and  $n$  are independently 0 or 1;

$Z$  represents hydrogen or a carbocyclic or heterocyclic ring of 5 to 7 ring atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 ring atoms;



Alk<sup>1</sup> and Alk<sup>2</sup> independently represent divalent C<sub>1</sub>-C<sub>3</sub> alkylene radicals;

X represents -O-, -S-, -S(O)-, -S(O<sub>2</sub>)-, -C(=O)-, -NH-, -NR<sub>7</sub>- where R<sub>7</sub> is C<sub>1</sub>-C<sub>3</sub> alkyl;

and wherein

Alk<sup>1</sup>, Alk<sup>2</sup> and Z when other than hydrogen, independently are optionally substituted by

(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>2</sub>-C<sub>3</sub>)alkenyl, or (C<sub>2</sub>-C<sub>3</sub>)alkynyl,  
 phenyl, optionally substituted by (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, halo, nitro,  
 amino, mono- or di-(C<sub>1</sub>-C<sub>3</sub>)alkylamino, cyano or trifluoromethyl;  
 monocyclic 5 or 6-membered heterocyclic, optionally substituted by (C<sub>1</sub>-  
 C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, halo, nitro, amino, mono- or di-(C<sub>1</sub>-  
 C<sub>3</sub>)alkylamino, cyano or trifluoromethyl  
 benzyl, optionally substituted in the phenyl ring by (C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy,  
 halo, nitro, amino, mono- or di-(C<sub>1</sub>-C<sub>3</sub>)alkylamino, cyano or  
 trifluoromethyl,  
 hydroxy, phenoxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, or hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 mercapto, (C<sub>1</sub>-C<sub>6</sub>)alkylthio or mercapto(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 oxo,  
 nitro,  
 cyano  
 halo  
 -COOH, or -COOR<sup>A</sup>,  
 -C(=O)NH<sub>2</sub>, -C(=O)NHR<sup>A</sup>, or -C(=O)NR<sup>A</sup>R<sup>B</sup>  
 -COR<sup>A</sup>, -SO<sub>2</sub>R<sup>A</sup>,  
 -NHCOR<sup>A</sup>,  
 -NH<sub>2</sub>, -NHR<sup>A</sup>, or -NR<sup>A</sup>R<sup>B</sup>,

wherein R<sup>A</sup> and R<sup>B</sup> are independently a (C<sub>1</sub>-C<sub>6</sub>) alkyl  
 group, R<sup>A</sup> and R<sup>B</sup> taken together with the nitrogen

atom to which they are attached form a 5- or 6-membered heterocyclic ring which may be substituted by (C<sub>1</sub>-C<sub>3</sub>)alkyl, hydroxy, or hydroxy(C<sub>1</sub>-C<sub>3</sub>)alkyl.

15. A compound as claimed in any of claims 1 to 13 wherein A is a group -NR<sub>8</sub>R<sub>9</sub> wherein R<sub>8</sub> and R<sub>9</sub> when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring of 5 to 8 atoms optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 ring atoms, any of which rings being optionally substituted by a radical of formula (II) as defined above.

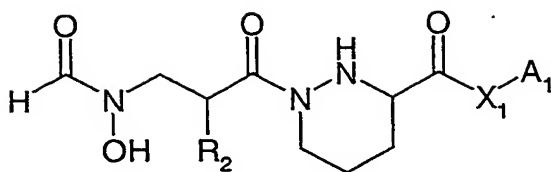
16 A compound as claimed in claim 15 wherein R<sub>8</sub> and R<sub>9</sub> when taken together with the nitrogen atom to which they are attached form an optionally substituted 1-pyrrolidinyl, piperidin-1-yl, 1-piperazinyl, hexahydro-1-pyridazinyl, morpholin-4-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl 1-oxide, tetrahydro-1,4-thiazin-4-yl 1,1-dioxide, hexahydroazipino, thiomorpholino, diazepino, or thiazolidinyl ring.

17 A compound as claimed in claim 15 wherein R<sub>8</sub> and R<sub>9</sub> when taken together with the nitrogen atom to which they are attached form an optionally substituted piperidin-1-yl or 1-piperazinyl ring.

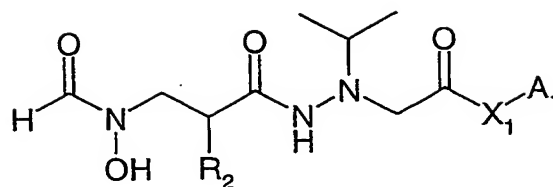
18. A compound as claimed in claim 14 wherein in the group (IV) Alk<sup>1</sup> and Alk<sup>2</sup> independently represent -(CH<sub>2</sub>)- or -(CH<sub>2</sub>CH<sub>2</sub>)-.

19 A compound as claimed in claim 14 or claim 18 wherein in the group (IV) m is 0, p is 1, and X is -C(=O)- or -S(O<sub>2</sub>)-.

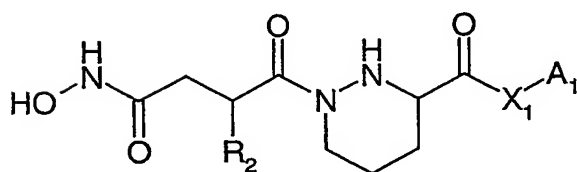
20. A compound as claimed in claim 1 of formulae (IIA) - (IID).



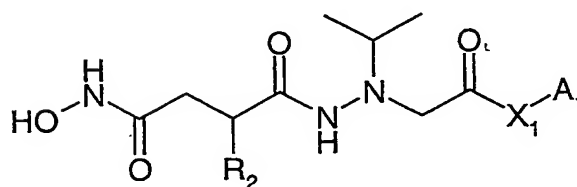
(IIA)



(IIB)



(IIC)



(IID)

wherein R<sub>2</sub> is as defined in any of the preceding claims;

X<sub>1</sub> is a bond, C<sub>1</sub>-C<sub>3</sub> alkylene, -NH- or -O-; and

A<sub>1</sub> is optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, cycloalkyl, aryl, or heterocyclic, for example methyl, ethyl phenyl, cyclopentyl, cyclohexyl, 2- or 3-furanyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-oxazolyl, or 3-, 4- or 5-thiazolyl, methoxymethyl, 3,5-bis-(trifluoromethyl)phenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 3,4-methylenedioxyphenyl, 4-fluorophenyl benzyl, 3-pyridyl, 4-pyridyl, cyclohexyl, 1,3-dimethylpyrazol-5-yl, 1-methylimidazol-5-yl, and 2-[morpholin-1-yl]pyrid-5-yl.

21. A compound as claimed in claim 20 wherein R<sub>2</sub> is n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl;

X<sub>1</sub> is a bond, -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -NH- or -O-; and

A<sub>1</sub> is methyl, ethyl phenyl, cyclopentyl, cyclohexyl, 2- or 3-furanyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-oxazolyl, or 3-, 4- or 5-thiazolyl,

methoxymethyl, 3,5-bis-(trifluoromethyl)phenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 3,4-methylenedioxyphenyl, 4-fluorophenyl benzyl, 3-pyridyl, 4-pyridyl, cyclohexyl, 1,3-dimethylpyrazol-5-yl, 1-methylimidazol-5-yl, or 2-[ morpholin-1-yl]pyrid-5-yl.

22. A method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound as claimed in any of the preceding claims.

23. The use of a compound as claimed in any of claims 1 to 21 for inhibiting bacterial growth in-vitro and in vivo in mammals.

24. The use of a compound as claimed in any of claims 1 to 21 for the manufacture of a composition for treating bacterial infection by inhibiting bacterial growth.

25. A method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound as claimed in any of claims 1 to 21 to the site of contamination.

26. A pharmaceutical or veterinary composition comprising a compound as claimed in any of claims 1 to 21 together with a pharmaceutically or veterinarily acceptable carrier or excipient.